Psychological Disorders After Stroke Are an Important Influence on Functional Outcomes
A Prospective Cohort Study

Robert West, DPhil; Kate Hill, PhD; Jenny Hewison, PhD; Peter Knapp, PhD; Allan House, DM

Background and Purpose—Psychological disorders are recognized as an important and common problem after stroke but little is known about their longer-term effects on functional outcomes. We investigated the trajectory of psychological symptoms after stroke and studied their impact on physical functional recovery.

Methods—The Stroke Outcomes Study was a prospective cohort study conducted in West Yorkshire, UK, from 2002 to 2006. Baseline assessments were conducted within 2 to 6 weeks of an index stroke event and follow-up at 9, 13, 26, and 52 weeks thereafter. Measures of psychological symptoms (assessed using the 28-item General Health Questionnaire) and function (modified Barthel Index) were completed at each visit. Longitudinal latent class analysis identified psychological symptom trajectories. Logistic regression modeled poor functional outcome. Multiple imputation was used as a sensitivity analysis.

Results—Five hundred ninety-two (55% of eligible patients) consented to participate. Four hundred forty-four (76%) complete sets of data (5 time points) were obtained for analysis. Four distinct classes of patients emerged from the analyses based on trajectory of psychological symptoms in the first 26 weeks after stroke. There was a strong association between functional outcome and class as defined by psychological symptom trajectory, which was not explained by age, sex, or initial disability after stroke.

Conclusions—Currently, the assessment of psychological distress is concentrated in the first weeks after stroke. Our results suggest that the timing of assessment and intervention needs to be reconsidered to take into account the trajectory of psychological symptoms rather than assessment at a single time point. (Stroke. 2010;41:1723-1727.)

Key Words: depression • functional recovery • outcomes • psych & behavior

Depression makes an important contribution to poor quality of life. It occurs in approximately one third of stroke survivors in the first months after stroke and antidepressant medication is widely used in clinical practice, but we know little about the longer-term effects of depression, or its treatment, on functional outcomes. One reason may be that the definition and measures used to characterize psychological disorder have an influence on findings. For example, in a previous study, we found no statistically significant association between diagnosed psychiatric disorder and mortality at 12 or 24 months after stroke but did find increased mortality associated with self-reported cognitive symptoms of psychological disorder. Another problem is that depression is not a static event-like exposure and yet few studies have explored the association between psychological symptoms as they evolve over time after stroke and later functional outcome. The study we report here was undertaken to clarify the impact of psychological symptoms on recovery from stroke taking into account the trajectory of those symptoms over the early months after stroke.

Methods
This prospective cohort study assessed the impact of early psychological symptoms on outcomes for patients with new or recurrent stroke. We identified patients admitted in 2 acute National Health Service Hospital Trusts in West Yorkshire, UK, between July 2002 and April 2005. Patients with transient ischemic attack, subarachnoid hemorrhage, or documented severe cognitive deficits were excluded. We used the Mini-Mental State Examination to screen all potentially eligible patients for cognitive function to ensure that they would be capable of undertaking the study assessments and outcomes measures. We applied a cutoff score of 25, although patients who were included if their low scores were clearly not due to cognitive impairment but to general frailty or a specific communication deficit (for example, word finding) that could be overcome. Patients were recruited prospectively and interviewed in the hospital, in care homes, or in their own residences. Poststroke effects may influence participation in research; thus, baseline interviews were conducted in a timeframe of 2 to 6 weeks after stroke, enabling psychological symptoms to be identified soon after the index event at the same time as accruing a reasonable number of participants. Consenting patients were seen 5 times in the year: T1 (2 to 6 weeks) and 4 additional time points: T2 (6 to 10 weeks), T3 (12 to 14 weeks), T4 (24 to 26 weeks), and T5 (52 weeks) after the index stroke. A full description of the
protocol for the Stroke Outcomes Study has been reported elsewhere. The study was conducted with the approval of the local research ethics committees for the 2 National Health Service Hospital Trusts from which patients were recruited. Written informed consent was obtained from all participants.

A comprehensive interview was completed at T1 to collect information on sociodemographic characteristics, physical functioning, and psychosocial measures. Relevant clinical information was obtained from medical records, and comorbidity was recorded using the Duke Severity of Illness Scale.

The self-reported 28 item General Health Questionnaire (GHQ28) was used to measure psychological symptoms. The GHQ28 has 4 domains (somatic, anxiety, social dysfunction, and depression) with 7 items in each. A number of scoring methods can be used; the most common are item-based scoring from 0 to 3 or dichotomized scores indicating presence (1) or absence (0) of a symptom. Higher scores represent greater symptom burden. In this study, we used the item-based scoring system (scored in the range 0 to 84). The cutoff for probable diagnosable psychological disorder using this scoring system is generally taken to be 40. A standardized semistructured psychiatric interview (the Present State Examination) was also conducted, which enabled us to explore the duration of key symptoms and especially of depressed mood. The Present State Examination interview was undertaken by trained research assistants working as a team. Regular briefing and standardization meetings maintained inter-interviewer reliability.

T5 (52-week) Barthel score was our main outcome variable with a maximum score of 20; lower scores indicate greater disability. The Modified Barthel Index (BI) was selected to assess physical functioning because despite its recognized ceiling effects, the BI is well understood in stroke research and other measures of function, for example, the Frenchay Activities Index, were found to be sex-biased in our sample.

Statistical Analysis
The primary aim was to investigate the impact of psychological symptoms measured by GHQ28 total score at 4 time points during the first 26 weeks after the index stroke on the physical outcome for patients (measured by their BI score at 52 weeks).

Our main independent variable (GHQ28) was repeatedly measured to assess the impact of psychological symptoms throughout rehabilitation. It would be desirable to include these repeated measures as covariates in the final model, but their high correlations would create problems with collinearity. As a solution, we chose to establish latent classes, that is, clusters of patients representing patterns of psychological symptoms during rehabilitation. We undertook the final regression on these latent classes rather than the repeated measures. This approach had the added benefit of yielding latent classes that described trajectories of psychological symptoms in patients with stroke so that the clusters themselves were useful secondary outcomes of the analysis.

Results
Study Participants
During recruitment, 3108 patients with stroke were identified in the study centers. One thousand seventy (34%) met the eligibility criteria and were invited to participate, of whom 592 (55%) gave consent. Four hundred eighty-four participants remained in the study to T5 (1-year follow-up). Mortality among consenting patients was 5% and 67 patients withdrew consent (a further 7 patients were withdrawn due to protocol violation). Some patients missed ≥1 follow-up visits during the course of the study, but 444 (76%) complete sets of data for all 5 time points were obtained for analysis.

The final sample comprised 253 (57%) males and 191 (43%) females. Median age was 71 years (range, 22 to 95 years). Severity of stroke was assessed by comparison between prestroke and poststroke BI measured at 52 weeks. The patients in the final sample had an average reduction in BI score of 3.6 points (SD = 4.9), a larger reduction showing greater reduction in function. One hundred ninety-one (43%) patients had no change in their BI score after the stroke, whereas 67 (15%) had experienced a change of ≥10 points. The sample therefore included a range of stroke severity but was biased toward patients with better physical function, almost certainly as a result of recruiting patients in the first few weeks after the index stroke event (when more severely impaired patients could not participate). Table 1 shows the baseline characteristics of the sample.

<table>
<thead>
<tr>
<th>Psychological Symptoms</th>
<th>No. (%) (N=444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living alone</td>
<td>143 (32.2)</td>
</tr>
<tr>
<td>Persistent depression</td>
<td>24 (5.4)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>89 (20.0)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>77 (17.3)</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>32 (7.2)</td>
</tr>
<tr>
<td>Aphasic</td>
<td>10 (2.3)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics of the Sample

Psychological Symptoms
At T1, the median GHQ28 total score was 21 (range, 0 to 81) with 95 patients (21%) scoring in the usual range for case definition (≥40). Ninety-four people (21%) were categorized with a potential diagnosis of psychological disorder according to the World Health Organization International Classification of Diseases, 10th Revision criteria assessed on the basis of the Present State Examination psychiatric interview. There was a steady decline in psychological symptoms during the course of the study so that by T5 median total GHQ score was 15 (range, 1 to 73) with 49 (11%) scoring a GHQ total of ≥40 and 53 people (12%) meeting the criteria for diagnosis of psychiatric disorder based on the Present State Examination interview.

Latent Classes
A longitudinal latent class analysis was undertaken (using Latent GOLD 4.0) on the GHQ28 total scores obtained from the patients with stroke at 4 time points: T1 to T4. Clusters of patients were formed around typical GHQ28 trajectories observed in the 3 to 26 weeks after the index stroke. The number of clusters was taken to be 4 because this optimized the Bayesian Information Criterion and yielded a useful representative summary of psychological status. Probabilistic assignment to cluster was used because it allows more flexibility in the model and more accuracy in the definition of psychological symptom trajectory as a covariate, but very similar results were obtained using modal assignment.

The 4 clusters (labeled 10, 14, 25, and 37) are shown graphically in Figure 1. The clusters are named according to their average 26-week GHQ score thus cluster 37 represents trajectories with an average mean GHQ score of 37 at the 26-week follow-up point. The trajectories show very similar trends: GHQ28 is higher soon after the stroke and decreases...
with time as the patient rehabilitates. Cluster 37 contains patients who are likely to be above the threshold for case-level symptoms for at least the first 3 months of rehabilitation. Using data from the psychiatric interview, we were able to ascertain the presence of depressive symptoms at least 2 years before the index admission. Persistent symptoms were more common in Clusters 25 and 37. Table 2 shows the age and sex mixes in the 4 clusters. The proportion of female patients increased with the characteristic GHQ28 level of each class.

**Physical Function**

We measured the physical function of patients using the BI score at 3 weeks after the index stroke (T1). The box plot (Figure 2) shows the distribution of the T1 BI scores in each of the clusters defined by the psychological symptom trajectories. For these analyses, the patients were placed into clusters by modal assignment; that is, patients were allocated to the trajectory that most closely resembled their responses. Generally, those with more psychological symptoms had poorer physical function immediately post-stroke, but there was a wide range of values. By the same token, patients in Clusters 25 and 37 were more likely to have a history of recurrent stroke and to have hemianopia identified on admission (Table 2).

The distribution (not shown) of BI scores at 52 weeks was highly skewed with many patients having the scale’s maximum value of 20. In Figure 3, the separate distributions of BI score at 52 weeks are shown against each of the psychological symptom trajectory clusters. Each cluster has some patients whose 52-week BI score is 20 and skew is also apparent but there are clear differences; Clusters 25 and 37 show worse outcomes at 52 weeks. The plot does not however take account of baseline (T1) BI score, the mixture of male and female, nor age. To adjust for different distributions of these variables between the classes, we undertook further modeling.

Physical impairment defined by BI score <20 at 52 weeks was taken as the dependent variable in a logistic regression on psychological symptom trajectory clusters, age, sex, and initial disability as defined by T1 BI. Once psychological symptom trajectory was included, there was no significant effect of sex, which suggests that its main influence might be through psychological status. The logistic model results are shown in Table 3. Cluster 10 is taken as the base level; that is, the effects of the other psychological symptom trajectories are seen in relation to Cluster 10. Patients are at greater risk of physical impairment 1 year after their index stroke if they are older, have more severe disability early after stroke, and if their psychological symptom trajectory over the 26 weeks after the stroke displays more persistent symptoms.

**Sensitivity Analysis**

We identified 3 types of dropout from our study: patients who died (n=33); patients who withdrew consent and refused

![Figure 1. Longitudinal latent classes/clusters based on GHQ totals at 4 time points. *Cluster 10: 26-week average GHQ score equals 10; Cluster 14: 14; and so on.](image)

![Figure 2. Baseline physical function by psychological symptom trajectory clusters.](image)

### Table 2. Characteristics of Latent Classes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cluster 10*</th>
<th>Cluster 14</th>
<th>Cluster 25</th>
<th>Cluster 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of patients modally assigned)</td>
<td>104 (23.4)</td>
<td>137 (30.8)</td>
<td>139 (31.3)</td>
<td>64 (14.4)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>70.0</td>
<td>69.1</td>
<td>70.9</td>
<td>67.2</td>
</tr>
<tr>
<td>Female</td>
<td>28.8%</td>
<td>40.1%</td>
<td>51.8%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Depressed mood (present &gt;2 years before stroke)</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Index stroke not lifetime first</td>
<td>16 (15%)</td>
<td>25 (18%)</td>
<td>24 (17%)</td>
<td>24 (38%)</td>
</tr>
<tr>
<td>Hemianopia (at admission for index stroke)</td>
<td>2 (2%)</td>
<td>7 (5%)</td>
<td>13 (9%)</td>
<td>10 (16%)</td>
</tr>
</tbody>
</table>

*Cluster 10: 26-week average GHQ score equals 10; Cluster 14: 14; and so on.
further follow-up (n=67); and patients who had missing values in their data but who had completed the study (n=41). The 7 patients withdrawn due to protocol violation were not included in the sensitivity analysis because they were either nonstroke or had a hemorrhagic stroke. The characteristics of the group who completed the study and the 3 categories of incomplete data are shown in Table 4.

Comparing the groups, we found that patients who died were older than the missing values group and the group who had completed all the visits, and had worse baseline function than patients in all 3 other groups and a higher proportion of recurrent stroke than either the completed group or the withdrawals.

To determine whether the characteristics of the participants with missing data had biased our results, and to what extent, a multiple imputation method using chained equations was applied to create estimated data sets using the R::mice library. A conditional distribution was specified for the missing data in each incomplete variable using predictors drawn from the existing data by regression analysis. The imputation process was replicated 5 times.15

The clustering exercise was repeated using the 5 imputed data sets. Strikingly similar rehabilitation patterns were observed in the estimated data sets, although there was some suggestion that the trajectory for the highest cluster might be raised by the inclusion of the dropouts being more likely to have increased psychological symptoms. Only slight differences were noted in the value of the asymptotes for the curves (Table 5). These findings are indicative of the overall consistency of the clustering approach.

### Discussion
Psychological disorder is commonly associated with stroke; our relatively less disabled cohort showed a prevalence of 21% at the first interview. We have also shown that persistent psychological symptoms in the first 26 weeks after stroke are associated with substantially poorer physical function outcomes at 52 weeks after adjustment for age, sex, and initial disability. The novelty of our approach has been the use of latent class analysis, which demonstrates the value of characterizing psychological disorder according to its trajectory in the first months after stroke.

This approach to identifying clinically important psychological disorder after stroke is challenging because it depends on repeated assessment to identify patients with a trajectory of persistent elevated scores. Figure 1 may be misleading to casual inspection because it might imply that an early high score predicts later high scores and therefore a single measure is sufficient for prediction. In fact, what it shows is the scores over time for patients assigned to certain classes according to their psychological symptom trajectory; class membership cannot be assigned on the basis of single observations. A similar observation has been made after myocardial infarction16 but without showing the same impact of persistent symptoms on outcomes.

In the format given in Table 3, it is not easy to assess the relative impact of psychopathology compared with age or stroke severity; the following comparisons, based on equating the effect size, may help. A unit decrease in BI score at 3 weeks is approximately comparable to the patient being 5 years older. The effect of being in Cluster 37 rather than

### Table 3. Logistic Regression of Physical Impairment at 52 Weeks

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year increase</td>
<td>1.04</td>
<td>(1.02–1.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>T1 BI per unit increase</td>
<td>0.76</td>
<td>(0.74–0.81)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Cluster 14</td>
<td>1.50</td>
<td>(0.66–3.41)</td>
<td>0.335</td>
</tr>
<tr>
<td>Cluster 25</td>
<td>2.96</td>
<td>(1.42–6.17)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cluster 37</td>
<td>9.23</td>
<td>(3.80–22.46)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

### Table 4. Characteristics of Cases With Missing Data

<table>
<thead>
<tr>
<th></th>
<th>Died</th>
<th>Withdrawn</th>
<th>Missing</th>
<th>Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>33</td>
<td>67</td>
<td>41</td>
<td>444</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>74.9</td>
<td>74.5</td>
<td>69.9</td>
<td>69.5</td>
</tr>
<tr>
<td>Female</td>
<td>39.4%</td>
<td>58.2%</td>
<td>29.3%</td>
<td>43.4%</td>
</tr>
<tr>
<td>Index stroke not lifetime first</td>
<td>13 (39%)</td>
<td>13 (19%)</td>
<td>14 (34%)</td>
<td>82 (20%)</td>
</tr>
<tr>
<td>Mean baseline BI</td>
<td>12.5</td>
<td>15.0</td>
<td>15.2</td>
<td>15.8</td>
</tr>
<tr>
<td>Mean baseline MMSE</td>
<td>25</td>
<td>26</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Depressed mood (present ≥2 years before stroke)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>23</td>
</tr>
</tbody>
</table>

MMSE indicates Mini Mental State Examination.
Cluster 10 is equivalent to the patient being 55 years older or having a stroke that is 10 U more severe on the BI scale. In these terms, the impact of psychological symptoms can be seen to be very substantial indeed.

**Alternative Models**

The distribution of the 52-week BI score prohibited modeling as a continuous variable. We therefore dichotomized the BI scores to 20 (no impairment in activities of daily living) and <20 (some physical impairment). Notwithstanding that a little information was lost, we decided to define physical impairment in this way and undertook a logistic regression. A more complex approach, for example, transformation of the data coupled with a mixture model like that used with zero-inflated modeling, might have retained full information, but our analysis clearly identified the key aspects in the data without this added complexity. For comparison purposes, a model with baseline GHQ in place of psychological symptom class was also considered. This alternative model explained far less deviance; thus, the model with psychological symptom class is strongly preferred (Akaike Information Criterion = 391.75 versus Akaike Information Criterion = 407.97).

**Limitations of the Study**

Longitudinal studies inevitably suffer from loss of data over their time course, particularly in chronic disease research in which deteriorating physical or cognitive status can impair patients’ ability to participate. Our study had virtually complete information at baseline but incomplete follow-up data due to the deaths, missed follow-up visits, failure/refusal to answer questions, or withdrawal of consent. The cluster analysis required complete data for each included case; thus, our initial approach was to exclude participants with missing values. Although this number (444) was sufficient to give ample power to the analyses undertaken, we decided to explore the characteristics of the remaining 141 participants in more depth because it is known that bias can be introduced when there is a probability that missing values are not completely random.17

Not surprisingly, we found a trend for older and less well patients to die during the course of the study. These patients were also harder to recruit and more likely to miss visits or withdraw if they did participate. The main limitation of our study therefore is that our cohort was relatively less disabled than the total population of stroke survivors. This is a difficult problem to address when researching chronic disease populations, but, given the substantial size of the effect we have shown, confirmatory studies are needed and research into its possible mechanisms.

**Clinical Implications**

The clinical implications of our study are 2-fold. First, it indicates that single assessment of psychological status will not be adequate in identifying those at risk of poor outcomes, a proposal supported by another recent study based on a more clinically oriented analysis of prognosis after myocardial infarction.18 Second, our results are a reminder that not all psychological disorder associated with stroke arises after stroke. Even when we restricted our analysis to the most persistent cases, it was clear that the classes with the most persistent and disabling psychological symptoms after stroke contained the majority of those cases of depression that had persistent depression before stroke. This phenomenon is often neglected in literature on “poststroke depression.”

Interventions to improve or prevent depression after stroke are relatively disappointing in their effects.9 Our results suggest that a more targeted approach might be beneficial, although the difficulty that clinicians face is that the patients most at risk for poor outcomes cannot be readily identified in the immediate postacute phase when most rehabilitation is undertaken.

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The Stroke Association UK provided the primary funding for this study.

**Disclosures**

None.

**References**

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/8/1723